## REMARKS

With entry of this amendment, claims 1-15 and 30-32 are pending in the application. Claims 16-29 were previously canceled, without prejudice, in response to a Restriction Requirement. By this amendment, claims 1-8 and 30-32 are amended for clarity in accordance with the Office's suggestions. These amendments are fully supported by the specification, and no new matter has been added to the application. Entry of these amendments and reconsideration of the application is respectfully requested.

### *Patentability Under* 35 *US.C.* § 102

Claims 1-5, 7 and 32 are rejected under 35 U.S.C. 102(b) as allegedly anticipated by Hussain et al. (US Patent 4,464,378, of record). Hussain et al. is cited for allegedly teaching "a nasal composition comprising analgesically effective amount of morphine wherein morphine may be in the form of acid addition salt." In addition, the Office states that Hussain "particularly teaches an aqueous nasal composition comprising 15% of morphine salt with pH at about 4.5."

Applicants respectfully traverse the foregoing rejection on the grounds that Hussain et al. fail to describe or enable the instantly claimed intranasal morphine formulations for eliciting an analgesic or anesthetic response.

Whenever the Patent Office relies upon a reference to support a rejection under 35 U.S.C. § 102, the Office bears the initial burden of demonstrating that the reference discloses all elements of the claimed invention.

> The factual determination of anticipation requires the disclosure in a single reference of every element of the claimed invention. . . .[I]t is incumbent upon the examiner to identify wherein each and every facet of the claimed invention is disclosed in the applied reference. Ex Parte Levy, 17 USPQ2d, 1461, 1462 (Bd.Pat.App.Int. 1990).

As was further explained by the Federal Circuit in In re Donohue, 226 USPQ 619, 621 (Fed. Cir. 1985):

> It is well settled that prior art under 35 U.S.C. § 102(b) must sufficiently describe the claimed invention to have placed the public in possession of it. (emphasis supplied).

Thus, proof of anticipation requires the Office to show that the reference provide a complete written description of the invention, and an enabling disclosure fully commensurate with the scope of the rejected claims. This standard was applied in Electronucleonics Laboratories, Inc. et al. v. Abbot Laboratories, 214 USPQ 139, 147 (N.D. Ill. 1981) (citations omitted), as follows:

> The standard for anticipation by patenting is the same one of a full enabling disclosure that applies to printed publications, i.e., it must disclose the invention in such full, clear and exact terms as to enable any person skilled in the art to which the invention relates to practice it.

In the instant case, the Hussain et al. patent provides neither a written description of Appellants' claimed intranasal morphine sulfate formulations useful for eliciting an analgesic or anesthetic response in mammals, nor an enabling disclosure that would serve to place the invention into the hands of the public of this invention.

Considering the facts of the instant case, Hussain et al. recite an extensive laundry list of compounds that they speculate may be useful within intranasal formulations for treating pain. In particular, Hussain et al. generically recite methods and formulations comprising, e.g.:

> [A]n analgesically effective amount of morphine, hydromorphone, metopon, oxymorphone, desomorphine, dihydromorphine, levorphanol, cyclazocine, phenazocine, 3-hydroxy-N-methyl-morphinan, lovophenacylmorphan, metazocine, nor-levorphanol, phenomorphan, nalorphine, nalbuphine, buprenorphine, butorphanol, levallorphan, or pentazocine, or a nontoxic pharmaceutically acceptable acid addition salt thereof . . ..

It is clear from the Hussain et al. specification that the inventors did not actually make any intranasal morphine solution--which is contrary to Office's assertions noted above. Specifically, the Office alleges that Hussain et al. "teaches an aqueous nasal composition comprising 15% of morphine salt with pH at about 4.5."

The relevant text of Hussain et al., however, reveals that no such solution was actually made. On the contrary, Example 2 of the Hussain et al. provides what appears to be a paper example for making a 150 mg/ml (15 mg/0.1 ml) solution of nalbuphine hydrochloride, wherein the pH is adjusted to 4.5 at an intermediate stage of making the formulation. In a subsequent passage, Hussain et al. discuss an even less-detailed, entirely speculative, procedure for making a morphine sulfate solution. Supposedly, the procedure for making the

nalbuphine hydrochloride formulation is "substantially repeated", and this yields "a nasal composition containing 15 mg of morphine sulfate per 0.1 ml."

Further in regard to the written description requirement, it is clear that Hussain et al. provides nothing more than a "shotgun" disclosure, and that the reference speculates on a large array of physicochemically distinct compounds that are hypothetically useful within intranasal formulations for treating pain. Example 1 relates to naloxone hydrochloride and apomorphine hydrochloride. Example 2 relates to nalbuphine hydrochloride and morphine sulfate, as noted above. Example 3 relates to naltrexone, levonantradol, butorphanol, and cyclazocine. Example 4 relates to naloxone, naltrexone, nalbuphine, levorphanol, buprenorphine, and levonantradol.

As the Federal Circuit's predecessor court held in In re Arkley, 455 F.2d 586,587-88 (CCPA 1972), an anticipatory reference must clearly and unequivocally disclose the claimed compound or direct those skilled in the art to the compound without any need for picking, choosing and combining various disclosures not directly related to each other by the teachings of the cited reference. Related legal authority cautions against reliance on so-called "shotgun disclosures" as evidence of anticipation or obviousness. See, e.g., In re Luvisi and Nohejl, 342 F.2d 102,144 U.S.P.Q. 646,650 (CCPA 1965), note 2:

> Our approach to this question [whether an expression which includes numerous species *ipso facto* discloses each and every one of those species] is to ask whether or not it can fairly and reasonably be said that one of ordinary skill in this art through a reading of the *entire* reference has constructive possession *the thing itself,* as opposed to possession of mere *language* which *embraces* the name of that thing. (Emphasis in original)

See also Ex parte Strobel and Catino, 160 U.S.P.Q 352 (Bd. Pat. App. & Int. 1968):

> We are of the view that the shotgun type disclosure of the reference ...would not guide one skilled in the art to choose appellants' restricted class of compounds from among the host of possible combinations and permutations suggested by patentees so as to make such class obvious within the meaning of 35 U.S.C. 103.

For all of the proposed formulations set forth in the paper examples of Hussain et al., it appears that the majority, if not all but one of them, were not actually made. The only working example of a nasal formulation actually made, and/or administered to a mammal relates to a naloxone formulation. This formulation was apparently administered to anesthetized Sprague-Dawley rats. Notably, the rats were intubated, and their nasal cavities

were sealed by adhesive to prevent natural drainage of the formulation (introduced by syringe) into the esophagus. The actual data from this example are limited to bioavailability data.

These limited data are not believed to be predictive of practical bioavailability of any nasal formulation for treating pain in mammals. Much less, the data for naloxone biovailability in this artificial model cannot reasonably be considered predictive of the bioavailability, nor efficacy for treating pain, of an intranasal morphine sulfate solution. Clearly, the single working example of Hussain et al. does not provide a written description, nor enabling support, for all of the shotgun list of compounds alleged by Hussain et al. to be useful within intranasal pain formulations. With respect to a morphine sulfate solution, this conclusion is particularly warranted on the basis that the only description provided is a paper example pertaining to nalbuphine hydrochloride, that is translated as a "substantially repeated" procedure to yield a 150 mg/ml morphine sulfate solution. The only actual description provided in this passage relates to the proposed concentration (150 mg/ml) of the hypothetical morphine sulfate solution. No direct description of the pH for a morphine sulfate solution provided, and it is further noted in this context that the pH for the hypothetical nalbuphine hydrochloride solution is adjusted to 4.5 at an intermediate stage of making the proposed formulation.

This does not amount to a written description nor an enabling disclosure of an intranasal morphine sulfate solution effective for treating pain in mammalian subjects, irrespective of the pH of the formulation. In this context, the Office is urged to consider that any aspect of an invention that is not explicitly disclosed in a reference cited under 35 U.S.C. § 102 must be inherent in the subject disclosure. This means that the subject matter "is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill." Continental Can Co. USA v. Monsanto Co., 20 USPQ2d (Fed. Cir. 1991). This cannot be said of the speculative pH value of a nalbuphine hydrochloride solution, the production of which is vaguely specified as being "substantially repeated" to yield an intranasal morphine sulfate solution. To find such disclosure to be "necessarily present" would constitute factual and legal error.

The record also clearly shows that the Hussain et al. disclosure fails to enable an intranasal morphine sulfate formulation having a pH in the range of about 3.0 to 7.0 effective for eliciting an analgesic or anesthetic response in mammal. In this regard, the Office's own

construction of the Hussain et al. disclosure is that it allegedly teaches "a 15mg/0.1mL solution (15%) ,of morphine at pH 4.5." Applicants respectfully submit that this is not an accurate interpretation, and that the proposed formulation would be inoperable and therefore facially non-enabled.

Briefly, the "substantially substituted" protocol of Hussain et al. for making a nalbuphine hydrochloride solution can not be followed to yield a solution of morphine sulfate in the manner proposed by the Office. Specifically, the Hussain protocol for nalbuphine hydrochloride teaches to combine 15 grams of nalbuphine hydrochloride with 80 mL of water, then to add enough sodium hydroxide solution to bring the pH of the composition to 4.5, then bring the solution to 100 mL with water. The facts presented in the previously filed Declaration of Dr. Steven Quay (filed July 9, 2001) clearly evince that this proposed formulation is inoperable:

> The statement in the `378 patent (Col. 10, Lines 45-49), that this procedure "is substantially repeated, except that 15 grams of morphine sulfate are used in place of the nalbuphine hydrochloride", teaches an inoperable protocol, and therefore cannot be interpreted in the strict manner proposed by the Office (Note: that the Office itself directly cites the Hussain `378 patent as teaching a morphine sulfate composition "containing 15 mg of morphine sulfate per 0.1 mL of water.") *The flaw in this interpretation of the `378 patent teachings is clearly revealed by the fact that the solubility of morphine sulfate in water would need to be at least approximately 150 mg/mL to achieve the formulation proposed by the Office* (by "substantial" substitution following the actual, nalbuphine hydrochloride procedure). *This solubility is grossly overestimated, and cannot be achieved under normal conditions at any pH. This defect is clearly elucidated by the following experiments conducted under my direction* and reported herein as follows: (italics added, underscores in original).

Dr. Quay's Declaration next provides detailed comparative experiments that in one part ("A") are directed to preparation of a morphine sulfate solution "Following Example 2 of U.S. 4,464,378 (as construed by the Office)." (Quay Declaration at ¶ 11). Specifically, 15 grams of morphine sulfate were mixed with 80 mL of water. The pH of the mixture was adjusted to 4.5 with dilute NaOH and stirred for two hours. The volume of the solution was made up to 100 mL with water. The results of this experiment are stated as follows:

> A clear solution was not obtained, indicating that 15 gm/mL of morphine sulfate is not soluble following the foregoing

procedure, including intermediate adjustment of the 80 mL solution to pH 4.5.

The second experiment ("B") provided in Dr. Quay's Declaration (at T 11) is directed to "Evaluation of Actual Solubility of Morphine Sulfate in an Aqueous Solution, Before and After pH Adjustment." To estimate the true drug solubility for morphine sulfate in an aqueous solution, the drug was added to water in small increments of about 0.5 gm each to obtain a saturated solution. After the solution was thus prepared, the volume of the solution was made up to 100 mL, and sufficient NaCl was added to adjust the solution to isotonicity. This procedure follows the Office's extrapolation of Example 2 of the `378 patent (directed to preparation of nalbuphine hydrochloride solution). The results of this experiment are summarized as follows:

> Result: The characteristics of the saturated aqueous formulation at 80 mL were as follows:
>
> Water = 80 mL
>
> Morphine Sulfate added: 4.342 gm + 0.529 gm
>
> NaCl added: 0.218 gm (calculated based on total amount of Morphine Sulfate added.)
>
> These findings indicate that the estimated solubility of morphine sulfate in water is about 50 mg/mL.

In a final experiment, the pH of the saturated morphine sulfate solution prepared in experiment "B" above was adjusted to 4.5, in order to determine the effects, if any, that the pH adjustment would have on solubilization of the morphine sulfate (saturated as indicated at about 50 mg/mL in the non-pH-adjusted solution). To assess this factor, the pH of the solution was adjusted incrementally by slow, stepwise addition of NaOH. After each addition of NaOH, the mixture was stirred for 30 min. (See, Declaration of Dr. Steven C. Quay, at ¶ 11). The result of this last experiment is stated as follows:

> Result: A clear solution of morphine sulfate from the solution set forth in subsection I), above, was not achieved at any elevated pH up to pH 8.12.

In light of these experimental findings, Dr. Quay aptly provides a factually irrefutable conclusion in his Declaration (at ¶ 12) that:

> *The foregoing experimental findings clearly demonstrate that the prophetic disclosure of the Hussain `378 patent regarding the preparation of a morphine sulfate solution (as strictly*

> *construed by the Office) is impracticable.* This demonstration casts serious doubt upon all of the teachings of this reference pertaining to morphine formulations, including the desired pH of such formulations for intranasal use, as these teachings have been interpreted by the Office. *The prophetic suggestion to make a blanket substitution of morphine sulfate for nalbuphine hydrochloride in a slavishly copied protocol, which is contrary to the skilled artisan's interpretation of the disclosure for the reasons noted above, renders an inoperable formulation.* Because it is impossible to obtain a morphine sulfate solution "containing lg-5 mg of morphine sulfate per 0.1 mL of water", *there can be no valid scientific significance assigned to any disclosure of a particular pH value of such an impracticable solution.* (italics added, underscore in original).

The fact that this construction of the prior art advanced by the Office would yield an inoperable combination clearly obviates the rejection under 35 U.S.C. § 102, and further represents compelling evidence of nonobviousness pertaining to the parallel rejection under 35 U.S.C. § 103, addressed below. In re Gordon, 733 F.2d 900, 221, USPQ 1125, 1127 (Fed. Cir. 1984).

In view of the foregoing facts and authority, Applicants respectfully request that the rejection of claims 1-5, 7 and 32 under 35 U.S.C. 102(b) as allegedly anticipated by Hussain et al. (US Patent 4,464,378) be withdrawn.

Claims 1-7 and 32 are rejected under 35 U.S.C. 102(b) as allegedly anticipated by Merkus (US Patent 5,756,483 of record). Merkus is cited for teaching "a pharmaceutical aqueous solution formulation of morphine for nasal delivery comprising about 5% of morphine salt at pH of 6." Merkus is also relied upon for allegedly teaching "applicant's preferred other pharmaceutical excipients, including a preservative, a phosphate buffer, a humectant, and an absorption enhancing agent."

Applicants respectfully traverse the foregoing rejection on the grounds that Merkus fails to describe or enable the instantly claimed intranasal morphine formulations for eliciting an analgesic or anesthetic response.

Considering in detail the teachings of the Merkus patent, Applicants contend that this reference actually teaches away from an effective, nasally administered morphine sulfate composition having a high ionization level, in the pH range from about 3.0 to about 7.0. Notably, the text of the Merkus disclosure cited by the Office (column 6, lines 37-50)

actually pertains to a study by Dutch authors (Verweij et al.) entitled "*Can morphine be administered nasally.*" (Merkus, at col. 6, lines 39-41). Contrary to the interpretation of this text by the Office, the Dutch study referenced in Merkus includes the notation "phosphate buffer (0.01 mol/L; pH 6.0)." As indicated in the Declaration of Dr. Steven C. Quay (at 118), "this notation specifies the pH of the phosphate buffer, not of the final formulation achieved by inclusion of the buffer." It is therefore improper to conclude from this notation that the Dutch study teaches any specific pH of a final morphine formulation for nasal administration as presently claimed. As stated by Dr. Quay, the referenced text "should not serve as a scientifically sound teaching relating to the pH of the final solution, only the buffer." (id.) Moreover, the Dutch study pertains to a morphine hydrochloride solution, not a morphine sulfate solution as presently claimed.

As noted above, for Merkus to anticipate the instantly claimed subject matter, it must provide a definite, written description of the invention that places the public "in possession of" the full scope of subject matter claimed by Applicants. This requirement is in conflict, however, with several aspects of the Merkus disclosure. In particular, Merkus specifically criticizes the Dutch study yielding a formulation that yielded undesirable results. In on critical aspect, Merkus states at column 6, lines 60-64 that:

> [T]he bioavailability of morphine after giving the nasal spray as described by Verweij and van Gijn is relatively low. After nasal absorption there is no first pass effect and therefore the nasal bioavailability should be higher than the oral. (underscores added).

Merkus thus notes with skepticism that the bioavailability of morphine delivered intranasally according to the Dutch disclosure was "relatively low". Therefore, to the extent that the Dutch study relates to aspects of Applicants' invention, Merkus teaches away from Applicants' formulations by criticizing the Dutch study. Merkus expressly describes the referenced formulation as an ineffective intranasal morphine solution. This evidence is summarized in the Declaration of Dr. Steven Quay, as follows:

> Accordingly, the Merkus disclosure actually teaches away from any disclosure in the Dutch reference regarding effective pH values for intranasal morphine solutions. Based on the Merkus disclosure, the proposed nasally administered morphine composition (including an unspecified amount of a phosphate buffer with a pH of 6.0) yields a morphine bioavailability that is substantially lower than the bioavailability of orally administered morphine, which would lead the artisan to administer morphine compositions orally, not nasally, and

would have been guided away from using nasally-administered morphine compositions incorporating a buffer designated to have a pH of 6.0.

In addition, Merkus further criticizes the formulation reportedly provided in the Dutch study by teaching that such formulations "are not stable". Among the principal parameters known to affect stability of chemical formulations is pH. Accordingly, for the combined reasons noted above the Office's reliance on the reported pH of a morphine solution in reference to the Dutch study is misplaced. By criticizing the stability of this reported formulation, Merkus implicitly teaches away from the reported pH for a useful morphine formulation.

For these reasons, it cannot be reasonably concluded that Merkus provides a full, enabling description of the instantly claimed invention, sufficient to have placed the public "in possession of" an intranasal morphine sulfate formulation having a pH within the claimed range and effective for eliciting an analgesic or anesthetic response in a mammalian subject. In this regard, the Office is further urged to consider that the Merkus specification appears to offer only speculative, conclusory statements concerning stability, bioavailabilty, and therapeutic efficacy for all of the reported formulations therein. These formulations include powder formulations and aqueous solutions alike, and all are reportedly enhanced in their stability and bioavailability, not by pH selection or any other modifications disclosed by Applicants, but by employment of cyclodextrin or other saccharides or sugar alcohols.

Also noteworthy, Merkus offers no actual working examples wherein any of the proposed formulations are evaluated and demonstrated to have the asserted stability, bioavailabilty, much less therapeutic efficacy for analgesic or anesthetic response. As such, the teachings relied upon by the Office should bear little or no evidentiary weight in determining issues of anticipate or obviousness with respect to the formulations, and their properties and results, exemplified in Applicants' disclosure.

In fact, as the Office expressly indicates in the instant Office Action (Paper No. 22, page 3, paragraphs 8 and 9), apart from the Dutch study reference Merkus "teaches various morphine formulations for nasal delivery wherein the pH has not be expressly indicated." With the exception that Merkus doesn't actually "teach" the prophetic formulations (particularly with respect to actual working examples showing stability, bioavailabilty, and therapeutic efficacy) Applicants agree that Merkus provides a prophetic "shotgun" disclosure

of various proposed formulations without any specific or practical guidance concerning useful pH values. When other teachings in the art are considered (as discussed below in the context of obviousness rejections), Merkus should actually be construed as teaching away from Applicants' formulations having the recited morphine sulfate, use, efficacy, and pH values.

Consistent with these facts, the Office expressly indicates in the instant Office Action (Paper No. 22, page 3, paragraphs 8 and 9), that, apart from the Dutch study reference, Merkus "teaches various morphine formulations for nasal delivery wherein the pH has not be expressly indicated." With the exception that Merkus doesn't actually "teach" the prophetic formulations (particularly with respect to actual working examples showing stability, bioavailabilty, and therapeutic efficacy) Applicants agree that Merkus provides a prophetic "shotgun" disclosure of various proposed formulations without any specific or practical guidance concerning useful pH values. In reference to the Dutch study, Merkus teaches away from the instantly claimed pH values. When other teachings in the art are considered (as discussed below in the context of obviousness rejections), these pH values and other aspects of the claimed formulations are neither disclosed nor suggested by Merkus, alone or in combination with other art of record. Collectively, this art should be construed as teaching away from Applicants' formulations having the recited morphine sulfate, use, efficacy, and pH values.

In view of the foregoing facts and authority, Applicants respectfully request that the rejection of claims 1-7 and 32 are rejected under 35 U.S.C. 102(b) as allegedly anticipated by Merkus (US Patent 5,756,483) be withdrawn.

Claims 8-15 and 32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Merkus (US Patent 5,756,483 of record) in view of The Merck Index (Eleventh addition, page 988-989). Merkus is cited for allegedly teaching a known pharmaceutical aqueous solution formulation of morphine for nasal delivery comprising about 5% of morphine salt at pH of 6. In addition, the Office contends that Merkus teaches morphine formulations containing applicant's preferred other pharmaceutical excipients, including a preservative, a phosphate buffer, a humectant, and an absorption enhancing agent. See, *e.g.*, column 6, lines 37-50.

As noted above, the Office concedes that Merkus teaches various morphine formulations for nasal delivery "herein the pH has not been expressly indicated." In addition, the Office states that "Merkus does not expressly teach a morphine formulation comprising all the ingredients herein (humectant, buffer, absorption enhancing agent, and thickening agent)." However, the Office asserts that all ingredients employed by Applicants "are known to be useful in morphine formulation for nasal delivery."

In specific reference to pH, the Office relies on The Merck Index for allegedly teaching "that the pH of aqueous solution of morphine sulfate and morphine hydrochloride is about 4.5 and 5 respectively."

Applicants respectfully traverse the foregoing rejection under 35 U.S.C. § 103(a) and submit that the invention of claims 8-15 and 32 is neither disclosed nor suggested by the teachings of Merkus in view of The Merck Index.

Considering first the teachings of the Merkus '483 patent, Applicants contend that this reference actually teaches away from an effective, nasally administered morphine sulfate composition having a high ionization level, in the pH range from about 3.0 to about 7.0, having sufficient bioavailability to be effective in the disclosed intranasal delivery methods for eliciting an anesthetic or analgesic response in mammalian subjects--for the reasons noted above. Generally, Merkus fails to describe and enable the instantly claimed subject matter, and in fact teaches away from Applicants' invention. The various teachings relied upon by Office, viewed in combination, fail to render the instantly claimed subject matter *prima facie* obvious, for the reasons presented above. Essentially, Merkus fails to disclose or suggest an effective pharmaceutical formulation of morphine sulfate having a high ionization level, at a pH from about 3.0 to about 7.0, that would have sufficient bioavailability to be effective in the disclosed intranasal delivery methods for eliciting an anesthetic or analgesic response in mammalian subjects.

Even if, however, a prima facie case of obvious was supported over the art of record, the instantly claimed subject matter provides "unexpected results" sufficient to render the claims patentable under 35 U.S.C. § 103. This latter conclusion is firmly grounded on the well-known principal that a drug's ability to be delivered systemically across mucosal surfaces generally depends on the degree of ionization of the subject drug. As described in the Declaration of Dr. Steven Quay (at ¶ 9):

> It was widely understood at the time of the invention that the degree of ionization of a drug influences the drug's ability to be delivered systemically across mucosal surfaces. The degree of ionization of a particular drug is largely determined by the drug's dissociation constant, the pKa, and the pH of the solution in which the drug is dissolved (The pKa of an acid is equal to the pH at which half of the molecules are ionized and half are neutral). A basic drug would be mostly in its unionized state when dissolved in a solution having a pH greater than the pKa of the drug. Accordingly, basic drug formulations are believed to be best absorbed from alkaline solutions where the pH is greater than the drug's pKa. In the particular case of intranasal formulation chemistry, it was a widely known teaching in the art that basic drugs generally show improved absorption across the nasal mucosa into the bloodstream when they are formulated in a basic solution having a pH greater than the dissociation constant of the drug. Therefore, for morphine formulations where the subject drug is a basic drug having a pKa of about 8.0, the artisan would generally have predicted the drug to be best absorbed when formulated in a basic solution, wherein the morphine would be delivered predominantly in its unionized state. (emphasis supplied).

Considering this evidence, it is clear that, for morphine formulations, the artisan would typically select a basic delivery solution as close to this value as possible to deliver the morphine predominantly in its unionized state. This general teaching contravenes the Office's position on an art-accepted, factual basis. This evidence is further explained in Dr. Quay's Second Declaration (at ¶ 10), as follows:

> Following this reasoning, the artisan would generally consider that solutions of morphine sulfate having a final formulation pH of greater than about 7.0 or 8.0 would allow for better absorption of morphine than lower pH solutions. For example, approximately 90% of the morphine sulfate in a solution having a final pH of about 9.0 would be expected to be in the preferred, unionized state (i.e., morphine free base). On this basis, such a high pH solution would be expected to provide for good absorption of morphine from the solution. In contrast, approximately 99% of the morphine would be predicted to be in an ionized state in a morphine sulfate solution having a pH of 6.0. A person of ordinary skill in the art generally would not have expected that morphine having such a high ionization level would provide for adequate absorption of the drug across the nasal mucosa into the bloodstream. The finding in the present invention that there is a high level of morphine absorption into the bloodstream when administered in formulations at pH 6.0 was therefore unexpected, and is clearly neither disclosed nor suggested by the art of record in the application. Similar results were shown for morphine sulfate at

> a pH range of about 3.0 to about 5.0 where over 99% of the morphine is also in an ionized state. (Underscores added).

Thus, the evidence of record strongly refutes the interpretation accorded by the Office to the cited references. In fact, the evidence of record, viewed in its entirety, teaches directly away from the instantly claimed subject matter. As explained in W. L. Gore & Associates, Inc. v. Garlock, Inc., 220 USPQ 303, 312 (Fed. Cir. 1983):

> He [the inventor] proceeded contrary to the accepted wisdom of the prior art by dramatically increasing the rate and length of stretch and retaining crystallinity. That fact is strong evidence of nonobviousness.

Applicants' results of providing a successful intranasal morphine sulfate delivery system characterized by a novel ionization state relating to distinct pH values must further be considered to constitute "unexpected" results--sufficient to overcome any *prima facie* case of obviousness deemed to be established by the Office. As explained by the Federal Circuit in In re Soni, 34 USPQ2d 1684, 1687 (Fed. Cir. 1995):

> One way for a patent applicant to rebut a prima facie case of unobviousness is to make a showing of 'unexpected results,' i.e., to show that the claimed invention exhibits some superior property or advantage that a person of ordinary skill in the relevant art would have found surprising or unexpected.
>
> ***
>
> [T]hat which would have been surprising to a person of ordinary skill in the art would not have been obvious. The principle applies most often to less predictable fields, such as chemistry, where minor changes in a product or process may yield substantially different results.

The unexpected nature of these results are in fact confirmed by the teachings of Merkus with respect to the Dutch (Verweij et al.) study, wherein Merkus criticizes the reported formulation (as interpreted by the Office) and therefore should be considered to teach away from the presently claimed invention. Based on the Merkus disclosure, the proposed nasally administered morphine composition (including an unspecified amount of a phosphate buffer with a pH of 6.0) yields a morphine bioavailability that is substantially lower than the bioavailability of orally administered morphine, and is "not stable". These teachings if construed according to the Office's interpretation would lead the artisan to administer morphine compositions orally, not nasally, and to select a pH distinct from the value suggested by the Office. Other evidence in this context is provided in extensive detail in the accompanying Declaration of Dr. Steven C. Quay, as summarized above.

With respect to The Merck Index, this reference fails to teach or suggest any element or limitation of Applicants' invention, apart from simple identification of the subject, active compound. In particular, The Merck Index does not teach any desired pH for a pharmaceutical formulation, of any kind, comprising morphine sulfate, particularly for intranasal administration. The Merck Index as relied upon by the Office merely teaches that simple aqueous solutions of morphine hydrochloride and morphine sulfate have respective pHs of about 4.8, and 5.0. This teaching with respect to a basic physicochemical parameter of morphine salts does not relate to an intranasal formulation, to stability, bioavailability, or efficacy of an intranasal morphine sulfate formulation for treatment of pain in mammals.

Because the facts of record are not believed to support a *prima facie* case of obviousness as alleged by the Office, the rejection of claims 8-15 and 32 are rejected under 35 U.S.C. 103(a) as allegedly unpatentable over Merkus (US Patent 5,756,483) in view of The Merck Index is respectfully submitted to be overcome. Additionally, or alternatively, the subject rejection under 35 U.S.C. 103(a) is believed to be overcome by the evidence above establishing "unexpected results" for the subject invention. Applicants provide an effective intranasal formulation of morphine sulfate at a high ionization level, at a pH within a distinct range of about 3.0-7.0, that is effective for eliciting an anesthetic or analgesic response in mammalian subjects. To sustain the instant rejection, the Office must provide factual evidence that is "inconsistent with" this evidence presented by Applicants (see, e.g., In re Marzocchi et al., 169 USPQ 367 (CCPA 1971)). Because such dispositive evidence does not appear in the record, withdrawal of the rejection of claims 16-29 under 35 U.S.C. 103(a) is earnestly solicited.

Now considering the rejection of claims 30-31 under 35 U.S.C. § 103 (a) over Merkus or Hussain et al., these references are also deficient under this Section of the Act for the reasons noted above in relation to 35 U.S.C. § 102. The Merkus and Hussain references are relied upon by the Office for the same alleged teachings, i.e., for disclosing a pharmaceutical composition of morphine for nasal delivery with an acidic pH in the range of Applicants claims. Applicants' remarks above, as supported by the Declaration of Dr. Steven C. Quay, obviate these stated grounds of rejection relating to the teachings of the Hussain et al. and Merkus references. The same deficiencies of these references identified above in the context of the rejections under 35 U.S.C. § 102 are respectfully submitted to obviate the instant

rejection of dependent claims 12 -13, and 30 -32 under 35 U.S.C. § 103. Additional grounds for obviating the rejection with respect to Merkus are set forth above.

With respect to Hussain et al., Applicants noted above that this disclosure is also largely a "shotgun", prophetic disclosure. The proposed method for making a nalbuphine hydrochloride solution is not expressly taught as a useful protocol for preparing a morphine sulfate solution. Rather, the nalbuphine hydrochloride protocol is disclosed hypothetically without working exemplification by Hussain as a method that can allegedly be "substantially repeated" for making a morphine solution. As set forth in the Declaration of Dr. Quay, at ¶ 8:

> [T]he term "substantially repeated" leaves open all unspecified conditions and parameters of the protocol to routine adjustment, particularly modifications aimed at tailoring the protocol to the specific characteristics of substitute compounds proposed for formulation according to the general protocol (e.g., morphine sulfate, and pentazocine lactate, each proposed as substitutes for nalbuphine hydrochloride). (emphasis supplied).

Thus, the reference presents, at best, an invitation to select alternate parameters and conditions, which clearly provides no more than an "obvious to try" teaching. As explained in In re O'Farrell, 7 USPQ2d 1673, 1681 (Fed. Cir. 1988) "[i]n some cases, what would have been 'obvious to try' would have been to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication or which parameters were critical or no direction as to which of many possible choices is likely to be successful."

Dr. Quay also critically points to conflicting teachings in the Hussain et al. patent that teach directly away from the intranasal morphine formulations proposed by the Office (e.g., having a supposed pH of 4.5 and a concentration of 150 mg/mL). In particular, the following quotation from the Hussain et al. disclosure (Example 5, at columns 11-12), is cited in Dr. Quay's Declaration (at ¶ 13):

> The following are illustrative aqueous solutions of selected drugs suitable for use as nasal drops or nasal spray. In each case, the pH of the final composition is adjusted to 7.4 . . .. (emphasis added).

In ¶ 14 of his Declaration, Dr. Quay emphasizes that:

> The first identified composition in this Example ('COMPOSITION A') is an aqueous intranasal formulation of nalbuphine hydrochloride. The teaching that the final pH of

> this nalbuphine composition is to be adjusted to pH 7.4, rather than pH 4.5, is facially inconsistent with the Office's interpretation of the protocol described in Example 2 of this reference, discussed above, and is consistent with my conclusion that the teachings regarding pH adjustment in Example 2 fail to convey a desired final pH adjustment to 4.5-for either a nalbuphine or morphine intranasal formulation.

In resolving these disparate interpretations of the Hussain et al. reference, the Office must view the facts from the standpoint of the skilled artisan—which clearly favors Applicants' construction of the Hussain et al. In this regard, additional testimony provided in the Declaration of Dr. Quay (at ¶ 8) shows that:

> Among the most likely parameters that would be considered for change in this context is adjustment of pH for a morphine sulfate, versus nalbuphine hydrochloride, solution. Simply put, the artisan would not presume from the cited passage that the `378 disclosure teaches a final pH of 4.5 for a morphine sulfate solution, even if one accepts the Office's position that the passage actually teaches this value for a nalbuphine hydrochloride solution. On the contrary, the artisan would more likely interpret the express qualification conveyed by the term "substantially repeated" in the passage, to leave the protocol open to such desired modifications as compound-specific pH adjustment. (emphasis added).

Considering the evidence of record in further detail, the skilled artisan would not have followed the teachings of Hussain et al. in the manner proposed by the Office--to select a pH for a morphine sulfate solution within the presently claimed range. This conclusion is firmly grounded on the well-known principal that a drug's ability to be delivered systemically across mucosal surfaces generally depends on the degree of ionization of the subject drug. The technical details of this principal are described above and in the accompanying Declaration of Dr. Quay (at ¶ 9). Considering this evidence it is clear, for morphine formulations where the subject drug is a basic drug having a pKa of about 8.0, the artisan would typically select a basic delivery solution as close to this value as possible to deliver the morphine predominantly in its unionized state.

Further considering the foregoing evidence, Applicants' results of providing a successful intranasal morphine delivery system characterized by the novel pH values presently claimed should be considered "unexpected" results sufficient to overcome any *prima facie* case of obviousness deemed to be established by the Office. As noted above, Dr.

Quay concludes that "the artisan would ordinarily have selected a considerably higher pH, e.g., greater than 7.0 or 8.0. in light of the knowledge summarized above concerning the pKa of morphine and the desirability of delivering drugs across mucosal surfaces in an unionized state."

The additional evidence provided in Dr. Quay's Declaration and elsewhere herein demonstrates clearly that the prophetic formulation method of Hussain et al., as construed by the Office, yields an inoperable result. The nature of this inoperable teaching relates to the solubility of morphine sulfate in aqueous formulations. To follow the Hussain et al. teachings for nalbuphine hydrochloride as advocated by the Office, the solubility of morphine sulfate in water would need to be at least approximately 150 mg/mL. As the data provided in Dr. Quay's Declaration clearly establish, this solubility is grossly overestimated, and cannot be achieved under normal conditions at any pH. These experimental findings clearly demonstrate that the prophetic disclosure of the Hussain et al. patent regarding the preparation of a morphine sulfate solution (as construed by the Office) is "impracticable." If the skilled artisan were in fact motivated to attempt to achieve the 150 mg/mL morphine solution by "substantially" following the nalbuphine hydrochloride protocol, the attempt would necessarily be considered a failure (it is of course not possible to nasally administer a solution that is approximately three-fold over-saturated!) This fact, that it is facially impossible to obtain a morphine sulfate solution following the disclosure of Hussain et al. for nalbuphine hydrochloride, indicates that there can be no valid scientific significance assigned to any disclosure of the reference regarding a particular pH value of an effective, intranasal morphine sulfate solution. These facts further evince that the subject matter of the instantly claimed invention yields "unexpected results".

In view of the foregoing facts and authority, the rejection of claims 30-31 under 35 U.S.C. § 103 (a) over Merkus or Hussain et al. is believed to be overcome.

## CONCLUSION

In view of the foregoing, Applicants believe that all claims now pending in this Application are in condition for allowance and an action to that end is urged. If the Examiner believes a telephone conference would aid in the prosecution of this case in any way, please call the undersigned at 425/455-5575.

Respectfully submitted

Dated: May 13, 2003

Jeffrey J. King
Reg. No. 38,515
Graybeal Jackson Haley LLP
155 - 108th Avenue N.E., Suite 350
Bellevue, WA 98004-5901
(425) 455-5575

## VERSION WITH MARKINGS TO SHOW CHANGES MADE

1. (Currently Amended) A pharmaceutical formulation for intranasal administration comprising morphine sulfate ~~or pharmaceutically acceptable salt thereof~~ at a pH from about 3.0 to about 7.0.

2. (Currently Amended) A pharmaceutical formulation according to Claim 1 comprising a therapeutically effective amount of morphine or sulfate ~~or pharmaceutically acceptable salt thereof~~ for eliciting an analgesic or anesthetic response in a mammal.

3. (Currently Amended) A pharmaceutical formulation according to Claim 1, further comprising morphine sulfate ~~or pharmaceutically acceptable salt thereof~~ in combination with a nasal delivery system.

4. (Currently Amended) A pharmaceutical formulation according to Claim 3, wherein morphine sulfate ~~or pharmaceutically acceptable salt thereof~~ is dispersed in an aqueous or non-aqueous formulation.

5. (Currently Amended) A pharmaceutical formulation according to Claim 4, wherein morphine sulfate ~~or pharmaceutically acceptable salt thereof~~ is at a concentration below about 50% w/w.

6. (Currently Amended) A pharmaceutical formulation according to Claim 4, wherein morphine sulfate ~~or pharmaceutically acceptable salt thereof~~ is at a concentration below about 10% w/w.

7. (Currently Amended) A pharmaceutical formulation according to Claim 4, wherein morphine sulfate ~~or pharmaceutically acceptable salt thereof~~ is dispersed in suspensions, solutions, powders, gels, ointments and creams.

8. (Currently Amended) A pharmaceutical formulation according to Claim 3, wherein the nasal delivery system comprises a buffer to maintain the pH of the morphine sulfate ~~or pharmaceutically acceptable salt thereof~~, a thickening agent, a humectant, an absorption enhancer and combinations thereof.

9. (Previously Amended) A pharmaceutical formulation according to Claim 8 further comprising one or more additional pharmaceutical excipients.

10. (Original) A pharmaceutical formulation according to Claim 8 further comprising a preservative.

11. (Original) A pharmaceutical formulation according to Claim 8, wherein the buffer is selected from the group consisting of acetate, citrate, prolamine, carbonate, phosphate and combinations thereof.

12. (Original) A pharmaceutical formulation according to Claim 8, wherein the thickening agent is selected from the group consisting of methyl cellulose, xanthan gum, carboxymethyl cellulose, hydroxypropyl cellulose, carbomer, polyvinyl alcohol, alginates, acacia, chitosan and combinations thereof.

13. (Original) A pharmaceutical formulation according to Claim 8, wherein the humectant is selected from the group consisting of sorbitol, glycerol, mineral oil, vegetable oil and combinations thereof.

14. (Original) A pharmaceutical formulation according to Claim 8, wherein the absorption enhancer is selected from the group consisting of sodium lauryl sulfate, sodium salicylate, oleic acid, lecithin, dehydrated alcohol, Tween, Span, polyoxyl 40 stearate, polyoxy ethylene 50 stearate, edetate disodium, propylene glycol, glycerol monooleate, fusieates, bile salts, octoxynol and combinations thereof.

15. (Original) A pharmaceutical formulation according to Claim 8, wherein the absorption enhancer is selected from the group of anionic, cationic and nonionic absorption enhancers and combinations thereof.

16. (Canceled) A method for eliciting an analgesic or anesthetic response in a mammal comprising nasally administering a therapeutically effective amount of morphine or pharmaceutically acceptable salt thereof at a pH from about 3.0 to about 7.0.

17. (Canceled) A method for eliciting an analgesic or anesthetic response in a mammal comprising nasally administering a therapeutically effective amount of morphine or pharmaceutically acceptable salt thereof at a pH from about 3.0 to about 7.0 to the mammal in combination with a nasal delivery system.

18. (Canceled) A method according to Claim 17, wherein the morphine or pharmaceutically acceptable salt thereof is dispersed in an aqueous or non-aqueous formulation.

19. (Canceled) A method according to Claim 18, wherein morphine or pharmaceutically acceptable salt thereof is at a concentration below about 50% w/w.

20. (Canceled) A method according to Claim 18, wherein morphine or pharmaceutically acceptable salt thereof is at a concentration below about 10% w/w.

21. (Canceled) A method according to Claim 18, wherein morphine or pharmaceutically acceptable salt thereof is dispersed in suspensions, solutions, powders, gels, ointments and creams.

22. (Canceled) A method according to Claim 17, wherein the nasal delivery system comprises a buffer to maintain the pH of the morphine or pharmaceutically acceptable salt thereof, a thickening agent, a humectant, an absorption enhancer and combinations thereof.

23. (Canceled) A method according to Claim 22 further comprising one or more pharmaceutical excipients.

24. (Canceled) A method according to Claim 22 further comprising a pharmaceutically acceptable preservative.

25. (Canceled) A method according to Claim 22, wherein the buffer is selected from the group consisting of acetate, citrate, prolamine, carbonate and phosphate and combinations thereof.

26. (Canceled) A method according to Claim 22, wherein the thickening agent is selected from the group consisting of methyl cellulose, xanthan gum, carboxymethyl cellulose, hydroxypropyl cellulose, carbomer, polyvinyl alcohol, alginates, acacia, chitosan and combinations thereof.

27. (Canceled) A method according to Claim 22, wherein the humectant is selected from the group consisting of sorbitol, glycerol, mineral oil, vegetable oil and combinations thereof.

28. (Canceled) A method according to Claim 22, wherein the absorption enhancer is selected from the group consisting of sodium lauryl sulfate, sodium salicylate, oleic acid, lecithin, dehydrated alcohol, Tween, Span, polyoxyl 40 stearate, polyoxyethylene 50 stearate, edetate disodium, propylene glycol, glycerol, monooleate, fusieates, bile salts, octoxynol and combinations thereof.

29. (Canceled) A method according to Claim 22, wherein the absorption enhancer is selected from the group of anionic, cationic and nonionic surfactants and combinations thereof.

30. (Currently Amended/Previously Added) A pharmaceutical formulation, according to Claim 1, for intranasal administration comprising morphine sulfate ~~or pharmaceutically acceptable salt thereof~~ at a pH of 3.5.

31. (Currently Amended/Previously Added) A pharmaceutical formulation according, to Claim 1, for intranasal administration comprising morphine sulfate ~~or pharmaceutically acceptable salt thereof~~ at a pH of 4.0.

32. (Currently Amended/Previously Added) A pharmaceutical formulation according to Claim 1, for intranasal administration comprising morphine sulfate ~~or pharmaceutically acceptable salt thereof~~ at a pH from about 5.0 to about 6.0.